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N-Boc Deprotection

Deprotection of *N*-*tert*-Butoxycarbonyl (Boc) Protected Functionalized Heteroarenes via Addition–Elimination with 3-Methoxypropylamine

Zachary Z. Gulledge[a] and Jesse D. Carrick*[a]

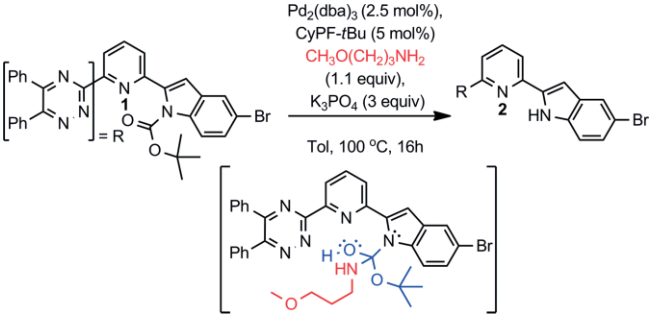
Abstract: Continued pursuit of functionalized soft-N-donor complexant scaffolds with favorable solubility and kinetics profiles applicable for the separation of the trivalent minor actinides from the lanthanides has attracted significant interest over the last three decades. Recent work from this laboratory resulted in the production of various *N*-Boc protected [1,2,4]-triazinyl-pyridin-2-yl indole Lewis basic procomplexants which necessitated the removal of the indole *N*-Boc protecting group prior to evaluation of complexant efficacy in separations assays. Traditional deprotection strategies involving trifluoroacetic and other protic and Lewis acids proved unsuccessful in removal of the recalcitrant indole-*N*-Boc protecting group necessitating the development of a new strategy for deprotection of this complexant class. A serendipitous result facilitated utilization of 3-methoxypropylamine as a mild deprotecting agent for various *N*-Boc protected heteroarenes via a proposed addition–elimination mechanism. Method development, application to various heteroarenes including indoles, 1,2-indazoles, 1,2-pyrazoles, and related derivatives, a ten-fold scale-up reaction, and experimental evaluation of a preliminary mechanistic hypothesis are reported herein.

Introduction

Functionalized heteroarenes with protected N-functionality are ubiquitous in alkaloid natural products,[1] pharmaceuticals,[2] materials,[3] and related compounds.[4] The *tert*-butyloxycarbonyl (Boc) and related carbamate protecting groups are commonly employed to diminish the nucleophilicity of sp^2-hybridized nitrogen atoms of indoles,[5] 1,2-indazoles,[6] pyrroles,[7] and related structures. As the pursuit of more complex, functionaly diverse structures continues to expand the need to develop differential protecting group installation and deprotection strategies concomitantly must evolve.

While completing a recent project[8] aimed at the formation of the pyridin-2-yl-indole C–C bond to afford procomplexants for potential employment in liquid–liquid separations[9] of minor actinides from lanthanides in simulated spent nuclear fuel, a series of functional group interconversions of **1** towards potentially improving solubility properties of prepared complexant scaffolds were undertaken (Scheme 1).

Pursuant to the aforementioned, the attempted Pd-catalyzed amination[10] of **1** failed to afford the desired indole amination product, but serendipitously yielded the Boc-deprotection product **2** via the proposed addition/elimination intermediate. Adjustment of reaction conditions, including additional equivalents of 3-methoxypropylamine, failed to afford the initially desired amination product. While initially disappointed with the lack of formation of the desired N–C bond via Pd-catalyzed amination, discovery of this transformation was a significant blessing given our previous inability to this point in the project to successfully deprotect the *N*-Boc group from the indole N-atom.



Scheme 1. Discovery of indole *N*-Boc deprotection method.

While electronic properties of the residual functionality of bonded *N*-Boc groups are important, recently reported results have postulated that ease of bond heterolysis in the case of conformationally strained amides can be attributed to ground state destabilization of the N–C=O bond via twisting, thus promoting cleavage.[11] The aforementioned phenomena can be readily exploited for downstream functional group interconversion of the amide bond via traditional addition–elimination with nucleophilic, primary amines[12] via tetrahedral intermediates.[13]

Further exploration and optimization of 3-methoxypropylamine as a mild, competent reagent for the *N*-Boc deprotection

[a] *Department of Chemistry, Tennessee Technological University, 55 University Drive, Cookeville, TN 38505-0001, USA*
E-mail: jcarrick@tntech.edu

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201901811.

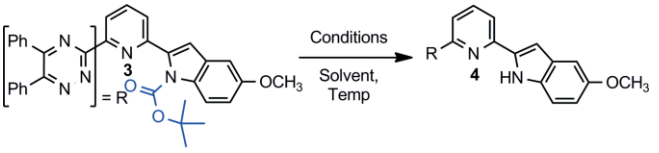
of various functionalized heteroarenes including tridentate [1,2,4]triazinyl-pyridin-2-yl indoles, 1,2-indazoles, 1,2-pyrazoles and related structures resulted in applicability to 25 diverse substrates. Method development, pyridinyl indole and Boc-protected heteroarene scope, as well as a scale-up experiment, and initial mechanistic interpretation of the transformation are reported herein.

Results and Discussion

The discovery of 3-methoxypropylamine as an effective reagent for the deprotection of **1** was a welcomed result as many previous attempts at deprotection of **3** under standard conditions proved futile.[14] Table 1 highlights selected experiments towards the deprotection of the *N*-Boc of **3** which were concurrently underway with the chemistry described in Scheme 1. Traditionally stalwart conditions for reliable *N*-Boc deprotection of sp^3, sp^2, and aromatic N atoms with trifluoroacetic acid,[15] nitric acid,[16] water,[17] and sodium methoxide[18] (entries 1–4) proved unproductive for the transformation of interest. Attempted reduction with lithium borohydride (entry 5) resulted in decomposition of **3** without substantive *N*-Boc deprotection. Reaction conditions employing trimethylsilyltrifluoromethane sulfonate in concert with 2,6-lutidine[19] afforded 90 % conversion of **3** to **4**. However, subsequent attempts to optimize this transformation towards reliable production and chromatographic isolation of **4** proved elusive. Further experimentation was attempted by employing standard Lewis acids including SiO_2,[20] CuI,[21] and LiCl[22] (entries 7–9) without success. $AlCl_3$[23] affected conversion of **3** to **4**, but with significant decomposition. Thermolytic degradation of the *N*-Boc group,[24] in addition to discrete treatment of **3** with trifluoroethanol,[25] were also unsuccessful. Realizing the result in Scheme 1 was commensurate with investigating the preliminary conditions described, a refocused approach to *N*-Boc deprotection of **3** via an addition–elimination strategy.

Pursuant to the aforementioned, an experiment was conceived which employed 3-methoxypropylamine (1.2 equiv.) in toluene at 50 °C to test the original hypothesis which afforded **4** in high conversion and good isolated yield after a modest 4.5 h reaction time. An amine screen was subsequently conducted to evaluate if alternatives existed to improve the desired transformation. In the case of 2-methoxypropylamine (entry 12) much slower conversion to **4** was observed relative to entry 11. Ethanolamine behaved similarly to entry 12 with lower conversion and extended reaction time. The discrete electronic environment in the case of 3-methoxypropylamine resulted in superior performance. Aliphatic and aromatic amines including octylamine (entry 14) and 4-*tert*-butylbenzene (entry 15), afforded slower conversion in the case of the former, and poorer conversion in the case of the latter. Hindered aliphatic amines, Huenig's base and the conjugate acid of LDA (entries 16–17) were attempted, and as expected, resulted in inadequate performance presumably due to steric hindrance of addition to the *N*-Boc carbonyl. With a preliminary set of reaction conditions defined for the transformation, focus shifted to the optimization of the *N*-Boc deprotection.

Table 1. Indole *N*-Boc deprotection method development.



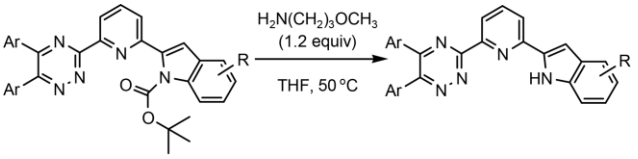
Entry	Reagent[a]	Equiv	Solvent	Temp [°C]	Time [h]	Result[b] [%]
1	TFA	360	Tol	50–90	6	**3**
2	1 M HNO_3	0.1	Tol	40	2	**3**
3	H_2O	555	CPME	100	12	**3**
4	$NaOCH_3$	0.2	CH_3OH	25	16	**3**
5	$LiBH_4$	1.1	THF	0–25	2	**3**[c]
6	TMSOTf, 2,6-Lut.	6.0	DCM	25	12	**4** (90 %)
7	SiO_2	–	MeOH	23	–	**3**
8	CuI	0.5	THF	0–50	16	**3**
9	LiCl	0.5	THF	0–50	16	**3**
10	$AlCl_3$	0.5	THF	0–50	16	**4** (99 %)[c]
11	3-methoxypropyl-amine	1.05	Tol	50	4.5	**4** (99 %)
12	2-methoxypropyl-amine	1.05	Tol	50	48	**4** (68 %)
13	ethanolamine	1.05	Tol	50	24	**4** (45 %)
14	octylamine	1.05	Tol	50	18	**4** (99 %)
15	4-*tert*-butylbenzyl-amine	1.05	Tol	50	24	**4** (5 %)
16	*N*,*N*-diisopropyl-amine	1.05	Tol	50	24	**3**
17	*N*,*N*-diisopropyl-ethylamine	1.05	Tol	50	24	**3**
18	3-methoxypropyl-amine	1.05	CH_3CN	50	18	**4** (99 %)
19	3-methoxypropyl-amine	1.05	DMF	50	48	**4** (80 %)
20	3-methoxypropyl-amine	1.05	THF	50	3	**4** (99 %)

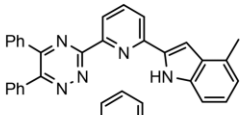
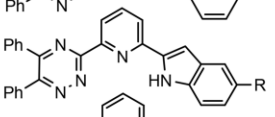
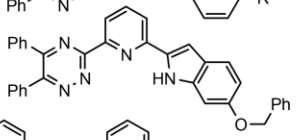
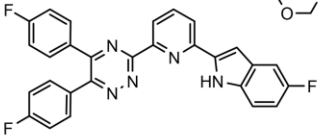
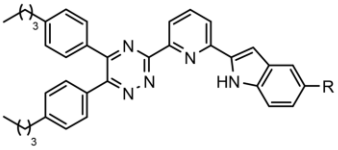
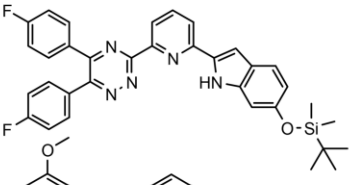
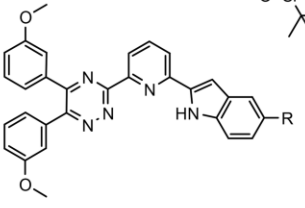
Reaction conditions: In an 8 mL reaction vial with magnetic stirring bar at ambient temperarture was charged: **3** (0.110 mmol), in solvent indicated (0.25 M), followed by reagent indicated, for temperature and time indicated. [a] Percent listed describes the ratio of **3** to **4**, in cases where **4** was afforded as determined by integration of selected aryl resonances in the crude ^1H NMR spectrum without internal standard. [b] Significant product decomposition was observed.

A solvent screen was conducted in various polar aprotic solvents with diverse dielectric constants (entries 18–20) with THF affording the cleanest conversion and minimized impurity profile of **3** to **4** while simultaneously resulting in the highest isolated yield. Temperature and concentration optimization attempts of the transformation did not improve upon previously defined conditions. Control experiments were also performed and underscored the necessity of both 3-methoxypropylamine and mild heating to afford **4**. With a seemingly viable method for indole *N*-Boc deprotection realized, efforts transitioned to the application to of this strategy to tridentate [1,2,4]triazinyl-pyridin-2-yl indole Lewis basic procomplexants delineated in Table 2.

Table 2 highlights the *N*-Boc-[1,2,4]triazinyl-pyridin-2-yl deprotection scope of the transformation. Synthetic access to the starting materials for this investigation have been previously reported.[8] A total of eleven examples in this area were evalu-

Table 2. Tridentate procomplexant *N*-Boc deprotection.

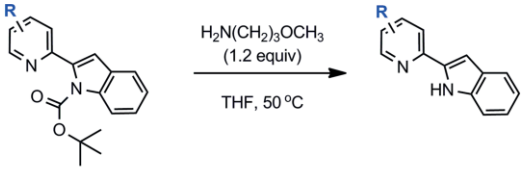


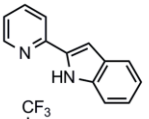
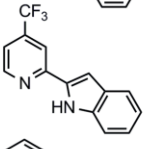
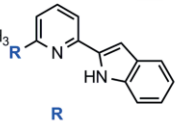
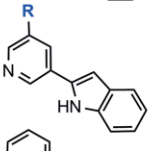
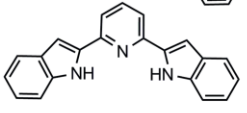
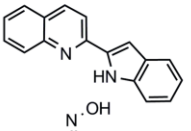
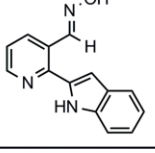
Entry	Product	Yield[a]
1		**5** (74)
2 **6** R = H 3 **2** R = Br 4 **4** R = OCH_3		**6** (52) **2** (19)[b] **4** (87)
5		**7** (74)
6		**8** (76)
7 **9** R = OCH_3 8 **10** R = F		**9** (77) **10** (84)
9		**11** (71)
10 **12** R = Br 11 **13** R = OCH_3		**12** (86) **13** (73)

[a] Reaction Conditions: Isolated, purified, and unoptimized yield. [b] Yield over two steps. [c] Percent listed describes the ratio of the starting material as determined by integration of selected aryl resonances in the crude ^{1}H NMR spectrum without internal standard. [d] Mixture of *E*/*Z* diastereomers.

ated for *N*-Boc deprotection with the optimized conditions described in Table 1. Phenyl substituents on the 1,2,4-triazine moiety, in concert with varied resonance and electron-donating functionality at the 4, 5, and 6 positions (entries 1–5),[8] afforded consistent performance with respect to deprotection with the exception of **2** where the lower isolated yield was a direct consequence of purification challenges. Examples which varied the functionality of the aryl substituents on the 1,2,4-triazine were evaluated subsequent. As such, inductively electron-withdrawing substituents in the 4,4′-positions of the 1,2,4-triazine (entries 6 and 9) afforded the desired products **8** and **11** in 76 % and 71 % yields, respectively. Fidelity of the *tert*-butyldimethylsilyl protecting group in the case of **11** was maintained. Entries 7 and 8 evaluated an aliphatic substituted 1,2,4-triazine with an electron-donating and electron-withdrawing substituent on the indole and resulted in achievement of the desired products **9** and **10** in good yield. The 3,3′-dimethoxy substituted 1,2,4-triazinyl moiety has afforded useful results in separations experiments of the minor actinides from lanthanides in simulated spent nuclear fuel.[26] This functionality in entries **10** and **11** also proved competent, affording **12** and **13** in similar yield. A consistent theme which emerged in the context of the diverse examples explored to this point in the project, which was further underscored as a function of additional examples below in Table 3 and Table 4, was that the main prerequisite for successful *N*-Boc deprotection of the indole moiety via addition–elimination with 3-methoxypropylamine was centralized on inductive-electron withdrawing groups situated in close proximity to the indole N-atom. With definition of a coherent strategy for deprotection of the procomplexants in Table 2 our attention turned to evaluating the *N*-Boc deprotection scope with other functionalized indoles (Table 3).

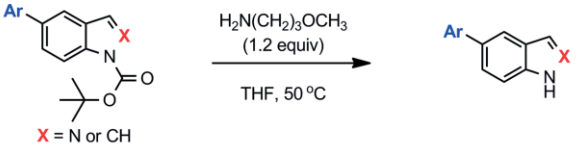
Table 3. Pyridinyl indole *N*-Boc deprotection scope.

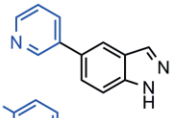
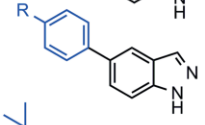
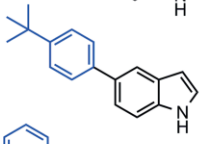
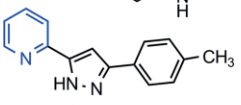
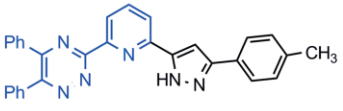
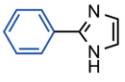


Entry	Product	Yield[a]
1		**14** (49)
2		**15** (73)
3 **16** R = 2-OCH_3 4 **17** R = 2-(CO)N$(CH_2)_3OCH_3$		**16** (45) **17** (92)[b]
5 **18** R = 5-OCH_3 6 **19** R = F		**18** (15)[c] **19** (0)[c]
7		**20** (46)[b]
8		**21** (77)
9		**22** (86)[d]

[a] Reaction Conditions: Isolated, purified, and unoptimized yield. [b] Yield over two steps. [c] Percent conversion after 48 hours from integration of selected resonances in the ^{1}H NMR spectrum without internal standard. [d] Mixture of *E*/*Z* diastereomers.

Table 4. Heterocycle *N*-Boc deprotection scope.



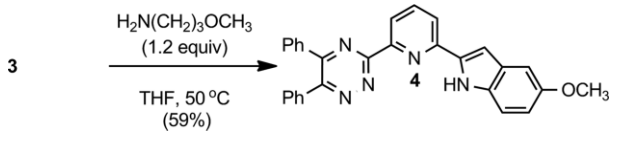
Entry	Product	Yield[a]
1		**23** (48)
2 **26** R = 4-*t*Bu 3 **27** R = 4-OCH_3		**24** (60) **25** (73)
4		**26** (0)[b]
5		**27** (38)[c]
6		**28** (22)[c]
7		**29** (55)

[a] Reaction Conditions: Isolated, unoptimized, purified yield. [b] Percent conversion after 72 h as determined from integration of selected resonances in the ^{1}H NMR. [c] Isolated yield for *N*-Boc protection and *N*-Boc deprotection of tautomers.

Examples in Table 3 sought to expand the method scope beyond the procomplexants delineated in Table 2 with various functionalized indoles.[27] Positional arrangement of an inductive electron-withdrawing functionality was critical to success in these cases. Pursuant to the aforementioned, entries 1 and 2 with pyridinyl connections to the indole moiety at the 2-position resulted in smooth *N*-Boc deprotection although the presence of an additional electron withdrawing group at C-4 on **15** afforded an improved yield. When a 6-methoxy substituent was present on the pyridine ring product **17** was afforded in 45 % yield. Carboxylic acid derivatives including the methyl ester and Weinreb amide[28] afforded the same product **17** in 92 % yield for the methyl ester over two steps via *N*-Boc deprotection and subsequent transamidation. Observing reaction progress for this discrete example via TLC, which was benchmarked by ^{1}H NMR, substantiated that the addition–elimination with 3-methoxypropyl-amine occurred first followed by subsequent *N*-Boc deprotection to afford **17**. Interestingly, in the case of the Weinreb amide starting material the product was afforded even though superficially a strong thermodynamic preference for the transamidated product would appear minimal. Entries 5–6 buttressed the positional arguments in entries 3–4 by evaluating substituted 3-indole pyridines. In these cases with intemperate disposition, the pyridinyl-N-atom relocated by one position made conversion to the desired *N*-Boc deprotected products painstakingly slow. A double *N*-Boc deprotection attempted in entry 7 resulted in **20**[8] in 46 % over two synthetic steps from the bis-protected starting material. Quinoline derivative **21** performed commensurate to previous 2-pyridinyl examples in Table 3. Deprotected pyridinyl oxime **22** was afforded in 86 % isolated yield over two steps including Suzuki–Miyaura cross-coupling and subsequent *N*-Boc deprotection as a mixture of greater than 95:5 *E*/*Z* diastereomers without observing the transimination product. Unfortunately, the described method was not successful with sp^3-hybridized *N*-Boc deprotections of several examples including *l*-*N*-Boc tryptophan, as well as *l*-bis-*N*-Boc tryptophan with unreacted starting material observed in both of the aforementioned cases. Having evaluated the impact of positional substituents on functionalized indoles we shifted application of the method to various heteroarenes of relevant interest which included an *N*-Boc protected moiety (Table 4).

Table 4 delineates examples focused on variation of the *N*-Boc protected heteroarene in the context of structures similar to the examples successful in Table 2 and Table 3 above. Focused on evaluating examples for which inductive-electron withdrawing functionality could facilitate a smooth transformation a series of 1,2-indazole derivatives (entries 1–3) were explored resulting in the desired products **23**–**25** in 48–73 % isolated yield. Further support for the necessity of activating the *N*-Boc group for deprotection with inductive-electron withdrawing functionality[29] is exemplified in entry 4 which is the indole analogue to successful 1,2-indazole **24**. In this example, sequestration of the additional N-atom proved deleterious to the formation of **26** with 0 % conversion observed after 48 hours. Other heteroarenes were evaluated including deprotection of *N*-Boc protected tautomeric 1,2-pyrazoles **27** and **28**[30] which were afforded in modest yields over two steps[31] via protection and deprotection. Deprotection of *N*-Boc protected imidazole was also successful under the reaction conditions affording 29 in 55 % isolated yield. It should be noted that the lower yields in this series of experiments can be attributed more to difficulty of isolation of pure compound via chromatography than poor performance of the transformation.

A tenfold scale up experiment (Scheme 2) was executed to ascertain the feasibility of material throughput via deprotection beyond the development scale transformation (Table 2). Conversion of **3** to **4** was realized in slightly lower yield than the development scale reaction.



Scheme 2. Tenfold scale-up experiment.

A preliminary mechanistic hypothesis for the *N*-Boc deprotection of functionalized heteroarenes is described below in Figure 1 based on initially acquired experimental spectroscopic data. Pursuant to the aforementioned, 3-methoxypropylamine is postulated to add to the *N*-Boc carbonyl resulting in tetrahedral intermediate **32** which eliminates carbamate **34** and the

weakly basic product (**33**) post proton transfer. Thermal degradation of the carbamate under the reaction conditions liberates CO_2 and affords *tert*-butanol and 3-methoxypropylamine.

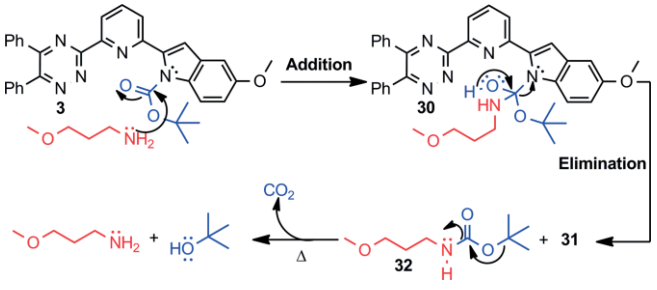


Figure 1. Proposed *N*-Boc deprotection mechanism.

As mentioned previously, when sub-stoichiometric amounts of 3-methoxypropylamine were added, incomplete conversion occurred, underscoring that the reaction is not perfectly catalytic with respect to the 3-methoxypropylamine. Observation of *tert*-butanol in crude reaction products post concentration under reduced pressure was observed, whereas **32** and 3-methoxypropylamine were not, suggesting azeotropic removal of the amine. Further, *tert*-butyl-3-methoxypropylamine also was not observed via ^{1}H NMR of crude reaction mixtures.

Conclusion

In summary, the authors have disclosed a mild *N*-Boc deprotection of various heteroarenes via an addition–elimination strategy with 3-methoxypropylamine leading to the production of **25** discretely successful examples, a ten-fold scale-up experiment, in addition to laying the groundwork for a preliminary mechanistic hypothesis. During the course of method development, the important role of inductive electron-withdrawing functionality proximal to the *N*-Boc group of interest was discovered to be critical to successful deprotection. The functional group scope of the transformation can be applied to a variety of N-heterocycles and the specificity of the developed method for activated, sp^2-hybridized heteroaryl N-atoms provides strategic opportunities for subsequent employment in complex molecule synthesis in which chemoselective *N*-Boc deprotection strategies are required. The tridentate complexants afforded from the method as described in Table 2 are currently being evaluated for efficacy in minor actinide separations and performance results will be disseminated in due course.

Experimental Section

General Considerations: All reagents were purchased from U.S. chemical suppliers, stored according to published protocols, and used as received unless indicated otherwise. All experiments were performed in oven- or flame-dried glassware. Reaction progress was monitored using thin-layer chromatography on glass-backed silica gel plates and/or ^{1}H NMR analysis of crude reaction mixtures. R_f values for compounds that resulted in a concentrically observed spot on basic alumina TLC plates are reported using the conditions listed. Melting point data listed is for a single, uncorrected experiment unless noted otherwise. All reported yields listed are for pure compounds and corrected for residual solvent, if applicable, from ^{1}H NMR spectroscopy unless otherwise indicated. Infrared spectroscopic data was acquired using attenuated total reflectance (ATR) from the (form) listed. All ^{1}H and ^{13}C NMR data was acquired from a 500 MHz multinuclear spectrometer with broad-band probe unless stated otherwise. *^{13}C NMR spectra acquired on a 500 MHz spectrometer with broadband N_2-cryoprobe were corrected for ring-down using linear back prediction via a vendor provided algorithm to improve baseline aesthetics. Chemical shifts are reported using the δ scale and are referenced to the residual solvent signal: $CDCl_3$ (δ = 7.26), $(CD_3)_2C{=}O$ (δ = 2.05), $(CD_3)OD$ (δ = 3.31), and $(CD_3)_2S{=}O$ (δ = 2.50) for ^{1}H NMR and $CDCl_3$ (δ = 77.16), $(CD_3)_2C{=}O$ (δ = 29.84), $(CD_3)OD$ (δ = 49.00), and $(CD_3)_2S{=}O$ (δ = 39.52) for ^{13}C NMR.[32] Splittings are reported as follows: (s) = singlet, (d) = doublet, (t) = triplet, (dd) = doublet of doublets, (dt) = doublet of triplets, (br) = broad, (br-d) = broad doublet, (br-m) = broad multiplet, (br-s) = broad singlet, and (m) = multiplet. High resolution mass spectrometry (HRMS) data was obtained utilizing electron impact ionization (EI) with a magnetic sector (EBE trisector), double focusing-geometry mass analyzer.

Supporting Information (see footnote on the first page of this article): Further detailed experimental procedures and copies of ^{1}H and ^{13}C NMR spectra as well as automated flash purification chromatograms are disseminated are available as supporting information.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

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Keywords: Deprotection · Aminolysis · Addition · Elimination · Heteroarenes

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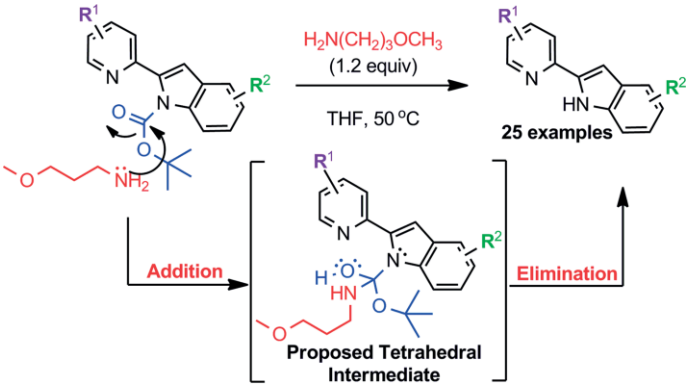
N-Boc Deprotection



The utilization of 3-methoxypropylamine as a mild deprotecting agent for various *N*-Boc protected heteroarenes via a proposed addition/elimination mechanism is described. Method development, application to various heteroarenes including indoles, 1,2-indazoles, 1,2-pyrazoles, and related derivatives, a ten-fold scale-up reaction, and experimental evaluation of a preliminary mechanistic hypothesis are reported herein.

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